COVER STORY

Comparing efficacy and safety of four intravenous sedation regimens in dental outpatients

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ABSTRACT

Background. Management of patients' fear and anxiety during dental treatment is a primary concern of dental practitioners. Pharmacological strategies used in outpatient dental settings must be both safe and effective. Regimens of intravenously administered sedative drugs were evaluated in a collaborative, multicenter study of outpatients undergoing removal of impacted third molars.

Methods. A total of 997 patients randomly received one of five treatments: placebo; midazolam administered to a clinical endpoint of conscious sedation (mean dose, 8.6 milligrams); midazolam plus additional midazolam as needed during the procedure (mean total dose, 12.2 mg); fentanyl (1.4 micrograms/kilogram) plus midazolam to achieve the same endpoint of conscious sedation (mean dose, 5.7 mg); or fentanyl (1.4 (μg/kg), midazolam (mean dose, 5.8 mg) and methohexital as needed during the procedure (mean dose, 61.0 mg).

Results. Each drug regimen reduced anxiety during surgery in comparison with placebo, with the combination of midazolam, fentanyl and methohexital resulting in significantly less anxiety in comparison with the other treatment groups. Pain reports by patients during surgery also were reduced significantly by the combination of fentanyl, midazolam and methohexital. Patients' global evaluations of the efficacy of sedation ranked midazolam with supplemental midazolam and the combination of fentanyl, midazolam and methohexital as significantly more efficacious than the other two drug regimens. The authors noted transient respiratory depression in patients in the two opioid-treated groups, but no other physiological changes were detected.

Conclusions. These data provide evidence that the drugs and doses evaluated resulted in therapeutic benefit to dental outpatients, with minimal incidence of potentially serious adverse effects.

Clinical Implications. The results of this large-scale study provide assurance to both the public and the dental profession of the safety of parenteral sedation with these drugs and combinations of these drugs when titrated slowly in the recommended doses by appropriately trained dentists.

Dentists have used pharmacological methods of pain control since the introduction of nitrous oxide and ether into clinical practice in the mid-1800s. However, the limitations of nitrous oxide and the potential morbidity and mortality associated with general anesthesia prompted dentists to seek alternatives in the form of sedative drugs that would enable the patient to remain conscious while pain was controlled via the concurrent administration of a local anesthetic.

The results of this large-scale study provide assurance of the safety of parenteral sedation with these drugs and combinations of these drugs.

In 1946, Jorgensen and colleagues[1] demonstrated that the combination of intravenously administered pentobarbital, meperidine and scopalamine resulted in sedation and analgesia persisting for three or more hours. This method of intravenous sedation represented a significant departure from the previous alternatives of local or general anesthesia. Other drugs used (alone or in combination) for parenteral sedation by dentists include opioids, benzodiazepines, ultrashort-acting barbiturates and antisialogogues, all with varying claims of efficacy or safety.[2-5] The drugs currently used most frequently for parenteral sedation in dental outpatients are a benzodiazepine (diazepam or midazolam), either alone or in combination with an opioid (fentanyl or meperidine), an ultrashort-acting anesthetic (methohexital or propofol) or both.[6]

Few reliable estimates of morbidity and mortality are available to support the claims of safety of parenteral sedation administered by dentists.[7] Clinician surveys[8-10] lack scientific rigor, and the results can, at best, be generalized only to the population of practitioners from which the samples are drawn. Although a consensus panel of experts[7] has stated that the use of sedative and anesthetic drugs in the dental office "has a remarkable record of safety," there are no reliable data to document this assertion.

Estimated mortality rates. A population-based study conducted in Great Britain from 1970 through 1979 estimated overall mortality associated with parenteral sedation to be approximately 0.5 to 1 per one million procedures.[11] It is unlikely that the drugs, doses and clinical practices of 20 to 30 years ago in Great Britain can be extrapolated to current use of parenteral sedation in the United States. A survey of mortality associated with general anesthesia and deep sedation performed by oral surgeons and dental anesthetists in Canada from 1973 to 1995 resulted in an estimated mortality rate of 1.4 per million cases.[12]

Few reliable estimates of morbidity and mortality are available to support the claims of safety of parenteral sedation administered by dentists.

Fear of dentistry persists despite the decreased incidence of dental disease and continuing improvements in pain control. The most common method of blocking pain during dental procedures—the intraoral injection of a local anesthetic—is aversive to many patients because of the pain associated with its administration and the perceived threat to well-being it represents. Several studies have documented that fear of dentistry leading to avoidance of dental care is a significant barrier to achieving oral health.[13-15] Fear of the pain of dentistry and of local anesthetic administration is magnified in young children, in emotionally and physically disabled patients, in patients undergoing an extensive surgical procedure and in patients who have become phobic because of previous unpleasant dental or medical procedures. As a consequence, patients continue to seek dental care performed with anxiolytic drugs, including parenterally administered sedation.

Need for large-scale collaborative study. The need for scientifically acceptable evidence to support the practice of anesthesia and sedation by dentists led several diverse groups to recommend prospective studies.[7,16,17] In response to these recommendations, the National Institute of Dental and Craniofacial Research, or NIDCR, initiated a large-scale collaborative study of prototypic parenteral sedation regimens. The objectives of the investigation were threefold:

- to assess the relative efficacy of prototypic sedative drug regimens used for dental outpatient sedation;
- to determine the incidence of common adverse drug reactions and premorbid physiological changes that may be predictive of serious adverse drug reactions;
- to establish standard research methodology for evaluating future therapeutic strategies for outpatient anesthesia and sedation.

This article summarizes the results of the NIDCR collaborative multicenter study. Our observations may be generalizable to the use of sedative drugs by dentists and to the use of the specific drugs and combinations evaluated for American Society of Anesthesiologists, or ASA, physical status P1 (healthy) and P2 (mild systemic disease) ambulatory patients. This large-scale, prospective, double-blind, randomized clinical trial provides evidence that the prototypic drug regimens evaluated are safe and effective when the drugs are titrated slowly to carefully monitored patients by appropriately trained dentists. These data provide a basis for the safe use of parenteral sedation by dentists in patients who would benefit from lowered anxiety or who would otherwise not tolerate the stress of dental procedures.

SUBJECTS AND METHODS

The collaborative multicenter study was performed simultaneously at five sites under contract with the NIDCR. Each site enrolled approximately 200 patients who were equally divided among the five treatment groups, for a total of 997 evaluable subjects. Dental clinic outpatients from the various sites who required the surgical removal of impacted third molars with parenteral sedation were invited to participate. The nature of the procedure and the research protocol were explained to patients, and they each signed an institutionally approved consent form. Demographic characteristics and baseline psychological and physiological variables were collected on a day before the oral surgery.

Anxiety. One of the investigators (there were at least three per site) measured each subject's anxiety toward dental procedures at the initial visit with the use of Corah's Dental Anxiety Scale, a four-item multiple-choice questionnaire that is sensitive to varying levels of apprehension toward dentistry.[18]

Inclusion and exclusion criteria. Inclusion criteria included the need for removal of two to four third molars, one of which was at least partially impacted in bone; anticipated surgical duration of 30 minutes; ASA physical status of P1 or P2; and a willingness to accept a 20 percent probability of undergoing oral surgery with local anesthetic only. Patients were excluded from participation if they were pregnant or lactating; had any systemic illness that increased the risks associated with outpatient oral surgery or parenteral sedation (for example, ASA physical status P3 [severe systemic disease that is not incapacitating]); reported a history of psychiatric illness or anorexia nervosa or the chronic use of central nervous system, or CNS, depressants, alcohol or antidepressants; exceeded standard weight table norms by more than 20 percent; reported any systemic infection or symptomatic teeth; or had any contraindications to the study medications.

The NIDCR study coordinator (R.D.) distributed a code to each institution's investigational pharmacy, and subjects were randomly assigned to one of five treatment groups on the basis of this code. The study medications were supplied to the investigators by the pharmacy in identically appearing syringes coded by patient number and the order of administration. Patients fasted for a minimum of six hours before the procedure.

Administration of parenteral drugs. An intravenous infusion was begun with a 20-gauge plastic catheter placed in the antecubital fossa or dorsum of the hand. An investigator collected preoperative psychological and physiological data, and a clinician initiated oxygen administration via nasal mask or prongs at a minimum rate of 3 liters/minute. The study medications then were administered by one of the investigators in the absence of the oral surgeon or any of the investigators involved in the assessment of the patient's subjective response to the surgical procedure. The oral surgeon and other investigators then entered the operatory and conducted the surgical procedure and collected the intraoperative data.

Drugs administered. The five treatment groups consisted of four active treatments and a placebo control. Fentanyl (50 micrograms/milliliter) was administered first in a fixed dose of 0.1 milligram per 70 kilograms body weight (1.4 (μg/kg) via slow intravenous infusion over two minutes; a matching saline placebo was administered to subjects in the treatment groups not receiving this opioid. Midazolam (1 mg/mL formulation), or a matching saline placebo, then was administered at a rate of 1 mL/minute until a clinical endpoint, characterized by slurred speech, patient self-reports of relaxation or drooping eyelids, was noted, or a maximum dose of 15 mL (equivalent to a maximum dose of 15 mg) was reached.

In the group receiving methohexital (10 mg/mL), a 1-mL bolus was administered after the midazolam titration and shortly before the local anesthetic was administered intraorally (patients in the other four groups received a 1-mL bolus of saline). A fourth syringe was available for the administration of boluses of 1 to 2 mL of saline, midazolam (0.5 mg/mL for the midazolam-plus-midazolam group) or methohexital (10 mg/mL for the midazolam, fentanyl and methohexital group), up to a maximum volume of 20 mL (equivalent to a maximum additional dose of 10 mg of midazolam or 200 mg of methohexital). The supplemental midazolam or methohexital was used as needed during the administration of the local anesthetic or during the oral surgical procedure if the patient's movements or vocalizations indicated that sedation was inadequate.

We chose midazolam as the prototypic benzodiazepine based on the results of a survey of dental practitioners who frequently use parenteral anesthesia and sedation in their practices.[6] Fentanyl was selected based on the results of the same survey,[6] which indicated that it is one of the most frequently used opioids in combination with a benzodiazepine. One treatment group received the combination of fentanyl, midazolam and methohexital. This regimen usually is characterized as producing "deep sedation," which is classified with general anesthesia in most state regulations and professional guidelines on the basis of the potential risk associated with this level of CNS depression. As used in this study, this drug combination allowed for adjustment of the sedative depth to meet the changing needs of the patient during the procedure, and served as a positive control for assessing the sensitivity of the study. Subjects in the placebo group received saline in all syringes to permit demonstration of the efficacy of the drug treatments and to serve as a control for responses owing to the stress of the procedure and administration of the local anesthetic.

Local anesthesia. Mandibular local anesthesia was produced via an inferior alveolar nerve block and infiltration of the long buccal nerve with 2 percent lidocaine and 1:100,000 epinephrine solution injected with a dental aspirating syringe. Maxillary local anesthesia was produced via infiltration of the posterior superior alveolar and greater palatine nerves with the same anesthetic solution. The oral surgeon tested the efficacy of anesthesia after five minutes by probing the mucosa over the third molar area, and patients reported anesthesia of the lower lip ("lip sign"). If patients were not adequately anesthetized, the oral surgeon reinjected the area and tested again for signs of anesthesia.

Assessment of pain and anxiety. The patient's subjective response to the stress of the surgical procedure was assessed at five minutes intraoperatively and at the completion of the procedure (or 30 minutes after the drugs were administered if the surgery was not completed by that time). Independent ratings of the patient's response to the procedure were made at these time points by the oral surgeon and by an investigator designated as an observer. Subjects remained at the clinic for 90 minutes after surgery, were provided postoperative analgesics (600 mg ibuprofen) and were dismissed from the clinic in the care of an adult. Subjects completed a questionnaire at 90 minutes and 24 hours evaluating their recall of the procedure and pictures of common objects shown to test amnesia.

Investigators asked subjects to estimate their anxiety by pointing to the term on a graphic rating scale[19] that "best describes how nervous you have been during the procedure." Pain was measured by asking the patients to point to a term on a similar graphic rating analgesic scale,[20] and by using a categorical scale that rated pain as none (scored as 0), slight (1), moderate (2) or severe (3). We deemed the use of a traditional paper-and-pencil visual analog scale infeasible during a pilot study because of drug-induced impairment of psychomotor function.

Ratings by surgeon and observer. The surgeon and observer independently rated the patient's level of alertness on a composite scale ranging from alert (5) to deep sleep (1). This scale has been demonstrated to be sensitive to the effects of benzodiazepines, combinations of benzodiazepines and opioids, and flumazenil, which reverses the effects of sedation.[21-24] The composite score is based on the subject's responsiveness to being called by his or her name, facial expression and presence of eye ptosis. The oral surgeon and observer also independently rated patient cooperation in terms of movements during administration of the local anesthetic and during the extractions, as follows:

- 0–no interfering movements;
- 1–minor movements, but patient's position remained appropriate;
- 2–minor movements that required repositioning of the patient;
- 3–movements that grossly interfered with the procedure.

The extent to which subjects verbalized discomfort during the procedure was rated independently by the surgeon and observer, as follows:

- 0–none;
- 1–some verbalization, but not indicating pain or discomfort;
- 2–some verbalization indicating pain or discomfort;
- 3–frequent complaints during the procedure.

Nonverbal signs of discomfort during the procedure were rated as follows:

- 0–none;
- 1–slight discomfort with occasional grimaces;
- 2–moderate discomfort, with feet or hands tensed, tears in eyes;
- 3–marked discomfort apparent frequently during the procedure.

Efficacy of sedation. The surgeon and observer independently rated the efficacy of the sedation as poor (0), fair (1), good (2) or excellent (3). Patients categorized their overall response to the sedative medication as poor (0), fair (1), good (2), very good (3) or excellent (4). At 90 minutes and 24 hours after surgery, subjects were asked if they recalled the following clinical events: placement of the intravenous catheter, the local anesthetic injections, the extractions or walking to the recovery room. They also were asked to identify from a composite of 12 pictures the three pictures shown to them before surgery, five minutes intraoperatively and at the conclusion of surgery. Subjects also were asked at 90 minutes and 24 hours about the occurrence and nature of any side effects.

The investigator tested ambulatory function

TABLE 1

DEMOGRAPHIC DATA AND SURGICAL VARIABLES.

TREATMENT GROUP	MEAN ± SD* MEASUREMENT										
	No. of Subjects		Weight (Kilograms)	Height (Inches)	Procedure Duration (Minutes)	Local Anesthetic† (Milligrams)	Dental Anxiety Trait Score‡	Surgical Procedure§			
	M**	F**						1††	16††	17††	32††
Placebo	115	90	70.4 ± 12.7	68.3 ± 4.1	25.2 ± 9.5	204.2 ± 74.4	8.1 ± 2.7	2.2 ± 1.1	2.1 ± 1.1	3.3 ± 0.7	3.3 ± 0.6
Midazolam	110	89	69.0 ± 13.9	67.4 ± 4.1	24.9 ± 9.0	196.1 ± 62.8	8.0 ± 2.7	2.3 ± 1.1	2.3 ± 1.1	3.2 ± 0.7	3.1 ± 0.8
Midazolam and Midazolam	98	96	68.5 ± 14.7	67.2 ± 4.1	25.0 ± 9.3	194.1 ± 71.4	8.2 ± 2.8	2.3 ± 1.1	2.3 ± 1.1	3.2 ± 0.7	3.2 ± 0.7
Midazolam and Fentanyl	93	92	69.9 ± 14.3	67.8 ± 4.1	24.4 ± 9.0	193.8 ± 71.0	8.6 ± 3.0	2.2. ± 1.1	2.1 ± 1.1	3.1 ± 0.7	3.2 ± 0.7
Midazolam, Fentanyl and Methohexital	116	86	68.5 ± 12.7	67.9 ± 4.0	25.2 ± 8.8	189.5 ± 66.2	8.0 ± 2.6	2.4 ± 1.1	2.3 ± 1.1	3.2 ± 0.7	3.2 ± 0.7

* SD: Standard deviation.
† Lidocaine.
‡ The scores range from 4 (relaxed) to 20 (frightened, physically sick). A mean score of 8 is equivalent to "a little uneasy" at the prospect of dental therapy.[18]
§ Simple extraction,1; soft-tissue impaction, 2; partial bony impaction, 3; full bony impaction, 4.
** M: Male; F: Female.
†† Tooth number.

before the sedative was administered and at 60 and 90 minutes after surgery. The results were categorized as follows:
- 1–able to sit for 10 seconds;
- 2–stands with support for 10 seconds;
- 3–stands without support for 10 seconds;
- 4–walks with support for six feet;
- 5–walks without support for six feet;
- 6–walks a straight line for six feet.

This gross measure of psychomotor impairment is sensitive to the effects of benzodiazepines and combinations of opioids and benzodiazepines.[21-24]

Physiological measures. A study investigator recorded the respiratory rate before and during administration of the drugs, at five-minute intervals during surgery, and at 60 and 90 minutes after surgery. Instances of apnea—defined as more than 30 seconds without a breath—also were recorded at these time points. Oxygen saturation was measured continually with a pulse oximeter (Ohmeda 3700 Oximeter), with simultaneous recording of expired carbon dioxide via nasal prongs (Ohmeda 5200 Capnometer). The investigator noted instances in which oxygen saturation fell below 92 percent or the expired carbon dioxide increased 25 percent above the baseline level as additional evidence of respiratory depression. A vital signs monitor (Dinamap model 8270, Critikon) was used to record blood pressure and pulse automatically on the same schedule as that above, and an electrocardiogram was monitored visually for the occurrence of any abnormal rhythms.

Physiological variables and continuous patient self-report measures, such as anxiety and pain, were analyzed via one-way analysis of variance, or ANOVA, with post hoc comparisons among treatment groups according to Duncan multiple range test. χ^2 tests were used to evaluate the incidence of recalling clinical events and pictures shown during the procedure, as well as the incidence of elevated carbon dioxide or lowered oxygen saturation. We analyzed categorical data via Kruskal-Wallis ANOVA, followed by nonparametric pairwise comparisons.

RESULTS

The distribution of sex, age, weight, height, procedure duration, local anesthetic dose and health status was similar across treatment groups. The mean dental anxiety trait scores approximate a response of "uneasy" at the prospect of dental treatment and are similar to the mean scores for two previous samples of college students.[18] The mean duration of surgery and the type of extractions performed also were similar across groups (Table 1). The similarity in these prognostic factors in regard to pain and anxiety during the procedure and the responses to anxiolytic drugs provide assurance that differences in outcome among the groups were due to the effects of the drug treatments under evaluation.

The total mean (± standard deviation, or SD) dose of midazolam administered to patients in the midazolam group (8.6 ± 3.2 mg) was similar to the initial dose administered to patients in the midazolam-plus-midazolam group (7.8 ± 3.2 mg) when titrated to the same clinical endpoint. An additional mean dose (4.4 ± 3.3 mg) of midazolam was administered to this second group during surgery, for a total dose of 12.2 mg. The midazolam dose titrated to the same endpoint was reduced in both of the following groups in which fentanyl was administered first: midazolam plus fentanyl group (5.7 ± 2.6 mg) and midazolam, fentanyl and methohexital group (5.8 ± 2.4 mg). The mean (± SD) dose of methohexital administered to the second group was 61 mg (± 47 mg). The mean dose of local anesthetic (2 percent lidocaine with 1:100,000 epinephrine) also was similar across groups (Table 1).

Anxiety levels. Patients in the placebo group reported a mean level of anxiety during the procedure that corresponded to the value for "tense, upset" (Figure 1). Patients in all four of the active treatment groups reported significantly less anxiety than did patients in the placebo group during the procedure. The administration of additional midazolam during the procedure did not seem to provide any further anxiety relief than that achieved when midazolam was only administered before the procedure, when assessed at five minutes intraoperatively or at the completion of surgery.

The addition of fentanyl or both fentanyl and methohexital resulted in greater anxiety relief at

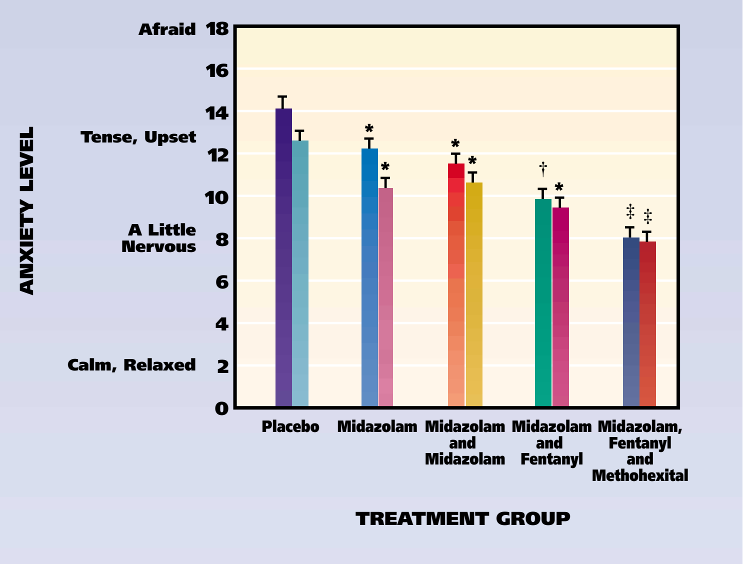

Figure 1. Mean (± standard error) patient self-reports of anxiety during oral surgery measured at five minutes intraoperatively (left bar) and at the completion of surgery (right bar) after administration of placebo; midazolam; midazolam and midazolam; midazolam and fentanyl; or midazolam, fentanyl and methohexital. The asterisk indicates $P < .05$ vs. placebo; dagger, $P < .05$ vs. placebo and midazolam; double dagger, $P < .05$ vs. the other four groups. The graphic rating scale ranges from 2 (calm, relaxed) to 42 (terrified).[19]

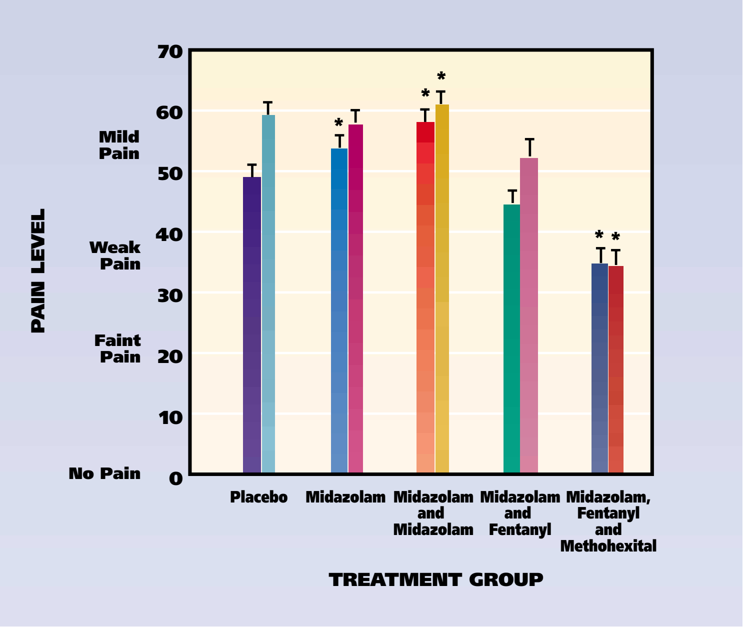

Figure 2. Mean (± standard error) patient self-reports of pain during oral surgery, as measured on a graphic rating scale at five minutes intraoperatively (left bar) and at the completion of surgery (right bar) after administration of placebo; midazolam; midazolam and midazolam; midazolam and fentanyl; or midazolam, fentanyl and methohexital. The y-axis shows the numerical values associated with the verbal descriptors for the lower end of the scale (the upper limit is 170 millimeters, which is maximum possible pain). The asterisk indicates $P < .05$ vs. placebo.

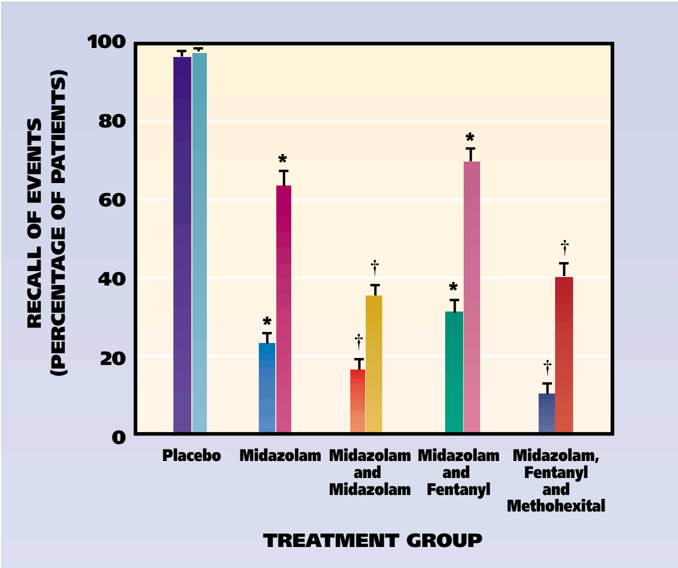

Figure 3. Patients' recall of local anesthetic administration (left bar) and tooth extractions (right bar) after administration of placebo; midazolam; midazolam and midazolam; midazolam and fentanyl; or midazolam, fentanyl and methohexital. The asterisk indicates *P* < .01 vs. placebo; dagger, *P* < .01 vs. placebo, midazolam, and midazolam and fentanyl.

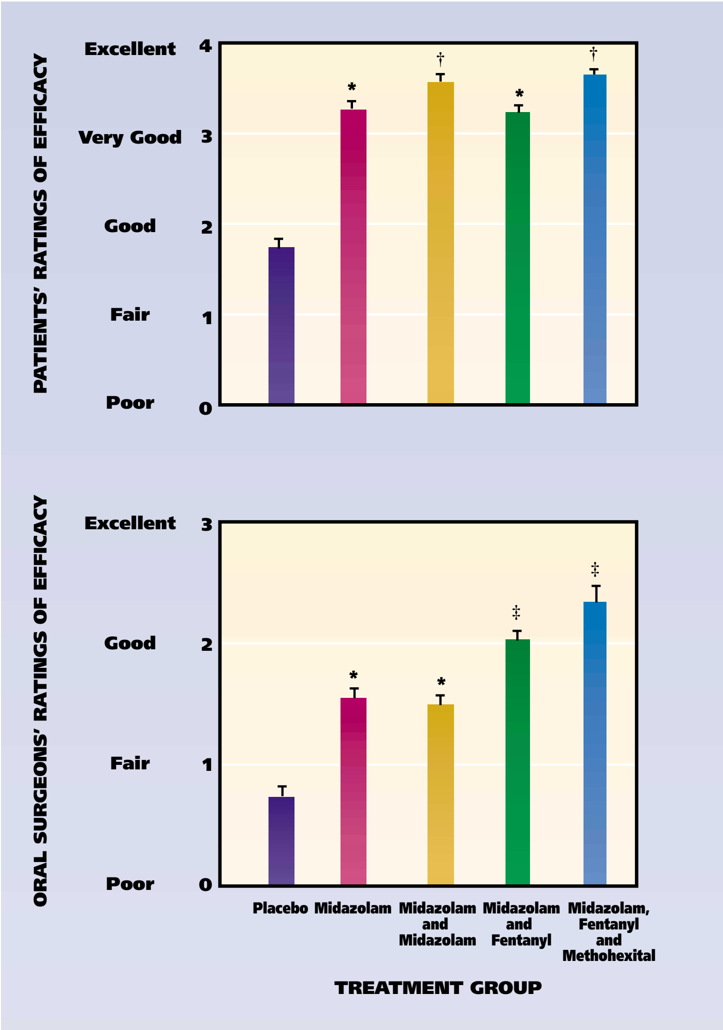

Figure 4. Patients' global evaluation of the efficacy of sedation (top) and oral surgeons' ratings of the efficacy of sedation (bottom) after administration of placebo; midazolam; midazolam and midazolam; midazolam and fentanyl; or midazolam, fentanyl and methohexital. The asterisk indicates *P* < .01 vs. placebo; dagger, *P* < .01 vs. placebo, midazolam, and midazolam and fentanyl; double dagger, *P* < .01 vs. placebo, midazolam, and midazolam and midazolam.

five minutes intraoperatively than the relief achieved when midazolam alone was administered. However, the difference in anxiety relief attributable to the addition of fentanyl was not significant when anxiety was assessed at the end of surgery. The combination of midazolam, fentanyl and methohexital resulted in significantly less anxiety at both evaluation times than the anxiety reported with the other three drug regimens and the placebo.

Pain levels. The level of intraoperative pain reported by patients was weak-to-mild, which represents approximately one-quarter to one-third of the maximal possible pain on the scale (Figure 2). The oral surgeon assessed the adequacy of local anesthesia before the start of the procedure by probing the mucosa over the teeth to be extracted and by questioning the patient about the presence of anesthesia of the lower lip; additional local anesthetic was administered if needed. Under these conditions, low levels of pain were experienced by all patients.

Patients in the two groups receiving only midazolam reported levels of pain at five minutes intraoperatively that were slightly, but significantly, higher than the mean level reported by patients in the placebo group. The combination of midazolam and fentanyl resulted in a mean level of pain similar to that of the placebo group. Patients in the three-drug combination group reported significantly less pain than patients in all other groups at both time assessments. We observed similar trends between groups for the four-point categorical scale (data not shown).

Recall of events. Amnesia in relation to the clinical procedure formed a basis for patients' belief that they had been unconscious during the procedure. As shown in Figure 3, patients in all drug groups reported significantly less recall of local anesthetic administration and extractions than did patients in the placebo group, who had nearly total recall of these events. The additional

TABLE 2

SURGEON AND OBSERVER RATINGS DURING THE SURGICAL PROCEDURE.

TREATMENT GROUP	MEAN ± SD* MEASUREMENT		
	Interfering Movements†	Verbalization of Discomfort‡	Nonverbal Signs of Discomfort§
Placebo	0.59 ± 0.78	1.35 ± 1.08	1.10 ± 1.01
Midazolam	1.01** ± 0.95	1.44 ± 1.05	1.22 ± 1.07
Midazolam and Midazolam	1.04** ± 1.02	1.47 ± 1.13	1.33** ± 1.09
Midazolam and Fentanyl	0.53 ± 0.73	1.06** ± 1.10	0.81** ± 0.98
Midazolam, Fentanyl and Methohexital	0.51 ± 0.81	0.65** ± 0.92	0.53** ± 0.77

* SD: Standard deviation.
† On a scale from 0 (no interfering movements) to 3 (grossly interfering movements).
‡ On a scale from 0 (none) to 3 (frequent complaints).
§ On a scale from 0 (none) to 3 (marked discomfort).
** $P < .05$ compared with placebo.

amnesia seen for the groups receiving supplemental midazolam or methohexital presumably is due to the maintenance of sedation by the additional medication administered during the procedure. A similar pattern was seen for the recall of extractions, but with a higher incidence of recall in all groups.

Patients' ratings of sedative efficacy. Figure 4 (top) illustrates patients' ratings of the efficacy of the sedative treatment. As the figure shows, patients detected a clear difference as a result of receiving supplemental midazolam or the combination of fentanyl, midazolam and methohexital, presumably because of the lower recall of intraoperative events reported by these groups. The overall evaluation of efficacy at 90 minutes was similar to that at 24 hours (data not shown).

Oral surgeons' ratings of efficacy. The oral surgeons rated the overall efficacy of the sedation at the completion of the procedure (Figure 4, bottom). These data indicate that all of the treatments provided a benefit to the patient over that of placebo, but that the rating of the efficacy of the drugs by the oral surgeons differed from the perception of the patients.

Patient movement. The oral surgeon and observer rated patient behavior during the administration of local anesthetic and during the surgical procedure on three categorical scales for movement, verbalization of discomfort and nonverbal signs of discomfort. Movements in all five groups ranged from no interfering movements to movements that grossly interfered with the procedure. The mean ratings for interfering movements were similar for the placebo, midazolam-plus-fentanyl, and three-drug combination groups (Table 2). Both of the midazolam groups had significantly more movement, with a mean rating of "minor movements with the patient's position remaining appropriate."

Verbalization of discomfort. As shown in Table 2, verbalization of discomfort ranged from none to frequent complaints during the procedure for all five treatment groups. The placebo, midazolam and midazolam-plus-midazolam groups received mean ratings between "some verbalizations not indicating pain" (scored as 1) and "some verbalizations indicating pain or discomfort" (scored as 2). The oral surgeon and observer gave the other two drug regimen groups significantly lower ratings for verbalization of discomfort.

Nonverbal signs. Nonverbal signs of discomfort ranged from "none" to "marked discomfort observed frequently during the procedure" for all five groups (Table 2). The mean ratings for the placebo and midazolam groups approximated "slight discomfort with occasional grimaces"

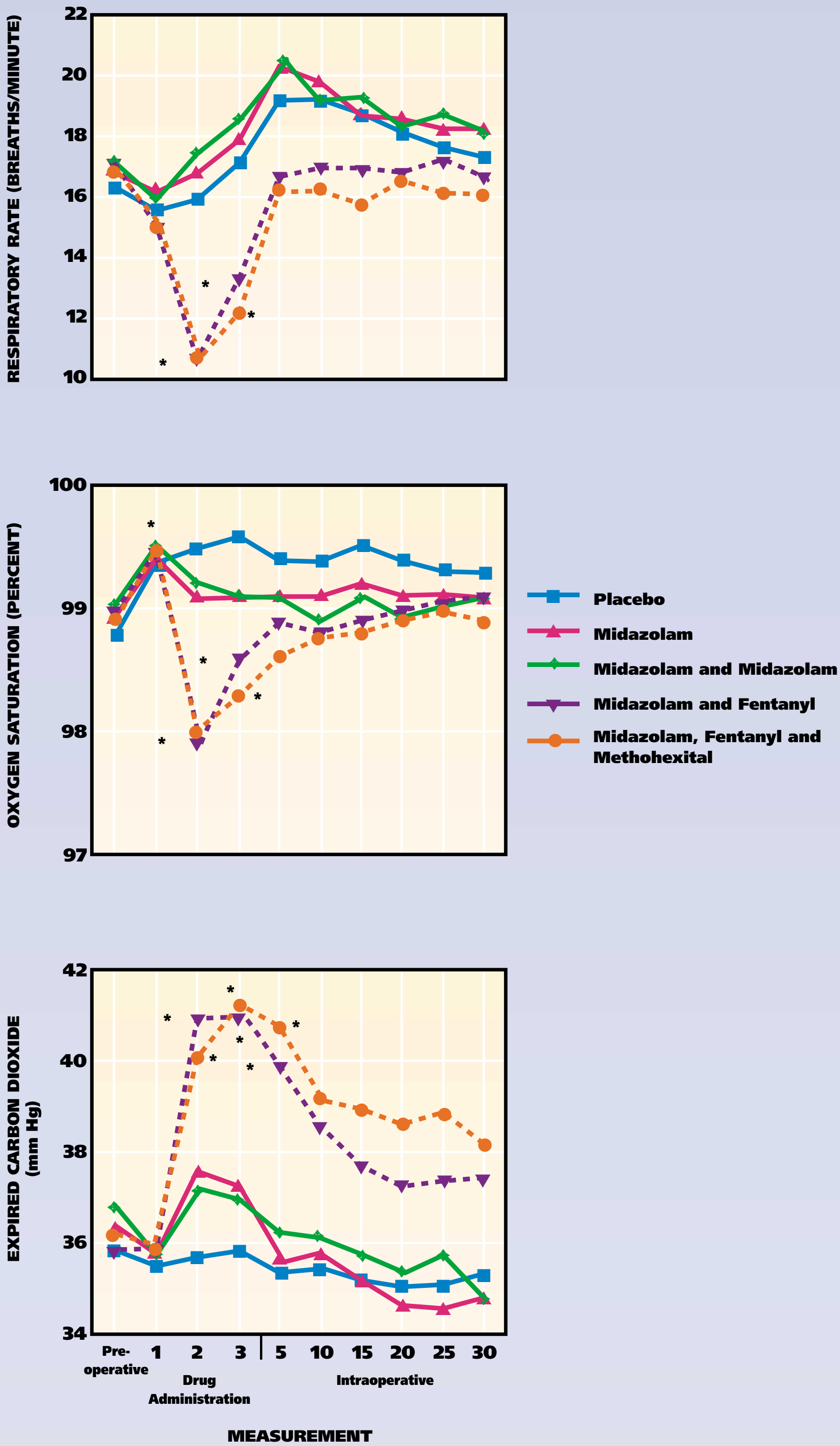

Figure 5. Patients' respiratory rate (top), oxygen saturation (center) and expired carbon dioxide (bottom) after administration of placebo; midazolam; midazolam and midazolam; midazolam and fentanyl; or midazolam, fentanyl and methohexital. The asterisk indicates $P < .01$ vs. placebo, midazolam, and midazolam and midazolam.

(scored as 1). The group receiving supplemental midazolam received a slightly higher, but significant, mean rating. The oral surgeon and observer gave the two fentanyl groups significantly lower mean ratings than the rating given the placebo group.

Respiratory rate. Respiratory impairment is the most frequently reported major adverse event associated with anesthesia and sedation in the dental office. Measurements of respiratory rate did not demonstrate any differences between placebo-treated patients and patients who received midazolam alone, even in the group that received supplemental midazolam (which resulted in a mean total dose of 12.2 mg) (Figure 5, top). Administration of fentanyl before midazolam did result in a decrease in respiratory rate from preoperative levels. The respiratory rate returned to preoperative levels during the surgical procedure.

Oxygen saturation. The oxygen saturation of blood, as estimated by pulse oximetry, was not affected by midazolam, but was decreased to a small extent (to 98 percent saturation) by the addition of fentanyl (Figure 5, center). Similarly, expired carbon dioxide was not affected by midazolam, but was elevated in the two groups that received fentanyl (Figure 5, bottom). Although oxygen saturation was similar in all groups during surgery, expired carbon dioxide levels remained slightly elevated in the midazolam-plus-fentanyl group and the midazolam, fentanyl and methohexital group, suggesting a continuing respiratory depression.

Transient apneic episodes. We observed no instances of transient apneic episodes (that is, more than 30 seconds without a breath) after administration of placebo, infrequent episodes after administration of midazolam

(3 to 7 percent of patients) and frequent episodes after administration of fentanyl (48 to 50 percent of patients). These data are consistent with the known pharmacology of opioid drugs. When the drugs are administered slowly and the patient is monitored carefully, the respiratory depression is transient and adverse events can be avoided.

Side effects. We observed no significant differences among the groups in regard to other measures of premorbid changes, such as blood pressure or heart rate (data not shown). The incidence of side effects elicited from patients at the end of surgery was low among the placebo group (6.7 percent); the frequency was elevated among the groups that received drugs, but did not differ substantially among the midazolam group (19.7 percent), the midazolam-plus-midazolam group (21.4 percent) and the midazolam-plus-fentanyl group (21.7 percent). However, the incidence of side effects was slightly higher for the group that received midazolam, fentanyl and methohexital (24.9 percent). Adverse events reported were primarily those that were consistent with the sedative property of these drugs (that is, drowsiness, incoordination, disorientation) and the stress of a minor surgical procedure (that is, syncope, nausea, vomiting).

Ambulatory function. We evaluated recovery of ambulatory function at 60 and 90 minutes after drug administration. The ability to walk without support for six feet (scored as 6) was impaired in all groups other than the placebo group (which scored 5.9) at 60 minutes (range of scores, 4.8 to 5.4). However, recovery was nearly complete in all active treatment groups before patients were dismissed from the clinic at 90 minutes (range of scores, 5.6 to 5.8).

DISCUSSION

These data provide evidence that the drugs and doses evaluated resulted in therapeutic benefit to adults, with minimal incidence of potentially serious adverse effects.

The intravenous administration of midazolam alone to about 400 adults under the conditions of the trial was effective in accomplishing the therapeutic objectives of anxiety relief and amnesia to traumatic or unpleasant experiences during treatment, without producing significant adverse events or premorbid changes. These findings, however, do not rule out the risk of serious sequelae from administering drugs too quickly, without appropriate physiological monitoring or professional supervision, or the possibility of idiosyncratic responses that can occur at a frequency that is too low to be detected in a sample of only 400 patients. Because of the young, healthy patient population evaluated in this study, these data cannot be directly extrapolated to medically compromised or elderly patients.

The administration of fentanyl followed by midazolam titrated to the usual clinical endpoint of drooping eyelids, slurred speech or patient reports of anxiety relief resulted in therapeutic advantage over midazolam alone, but with transient respiratory depression. We can attribute greater anxiety relief, marginally less pain and better intraoperative conditions to inclusion of this opioid administered only at the beginning of the surgical procedure. Patients, however, did not report any overall advantage of the fentanyl-plus-midazolam combination in comparison with the groups that received midazolam alone. Moreover, these therapeutic benefits were accompanied by transient episodes of apnea in approximately half of the subjects, although they posed no problem in this young, healthy study sample. However, this finding suggests that the therapeutic benefits of an opioid must be weighed against the increased possibility of transient respiratory depression.

The combination of midazolam, fentanyl and methohexital is characterized as deep sedation,[7] and can result in a level of CNS depression greater than the level of sedation usually described as conscious sedation. In this study, patients clearly detected a therapeutic advantage to this drug combination when used for conscious sedation in terms of anxiety relief, intraoperative pain control, amnesia and the global evaluation of efficacy. The oral surgeons also rated this drug combination as most effective. These therapeutic advantages were associated with decreased respiratory rate, transient apnea in 50 percent of the sample, slightly decreased oxygen saturation and transient carbon dioxide retention. These data support the National Institutes of Health expert opinion[7] that the therapeutic benefits of this sedative regimen over lighter levels of sedation must be balanced against the potential for morbidity that accompanies greater levels of CNS depression and requires greater training of practitioners who administer the drugs.

This investigation represents the largest prospective clinical study evaluating the efficacy and safety of parenteral sedation in dental outpatients. In general, these observations should provide assurance to both the public and the medical and dental professions of the safety of parenteral sedation with these drugs and combinations when administered slowly via titration in recommended doses. These findings also confirm the need for careful monitoring to detect premorbid changes that can accompany the therapeutic effects of opioids and barbiturates and possibly result in significant morbidity if not detected early.

However, even a study as large as this one does not provide adequate information about adverse events that occcur at a frequency too low to be evaluated in 1,000 patients. Future investigations should address the frequency of adverse events in large-scale prospective studies to provide a broader scientific basis for evaluations of safety in the use of parenteral sedation in dental outpatients. Potentially rich sources of data for assessing factors associated with morbidity and mortality are dental schools and other institutions that manage a large number of cases of general anesthesia and parenteral sedation.

A use of parenteral sedation analogous to dentistry is gastrointestinal endoscopy. A large-scale study (more than 20,000 cases) yielded an estimated incidence of serious cardiovascular complications of 5.4 per thousand cases and a mortality rate of 0.3 per thousand cases.[25] These data identified the concomitant use of opioids with a benzodiazepine as a factor contributing to morbidity and mortality. The incidence of mortality was similar to estimates of mortality associated with inpatient general anesthesia: one to three deaths per 10,000 procedures.[26]

A retrospective survey of physicians in the United Kingdom who performed gastrointestinal endoscopy identified factors associated with 52 deaths among 1,048 practitioners during a two-year period.[27] This mortality rate differs from the generally low rates of mortality attributed to outpatient use of general anesthesia by dentists, which range from 1 in 284,000 cases[11] to 1 in 840,000 cases.[9] Prospective data from dental outpatients are needed to provide credible evidence that these discrepancies are real, and can be attributed to such factors as a healthier population of dental patients than patients in whom anesthesia and sedation are produced on an inpatient basis, the decreased likelihood of anesthetic complications with shorter-duration outpatient procedures, the effect of state regulations governing the use of sedative agents in dentistry, and the safety of conscious sedation in comparison with that of general anesthesia.

There are limitations to the direct extrapolation of these findings to clinical practice. First, the patient sample was selected to include only young healthy adults rather than to represent the total population of patients undergoing sedation in the dental office. While such patient selection is appropriate for a controlled clinical trial, prospective studies that include the young, the elderly, patients with preexisting disease and patients being treated with other medications are needed to provide evidence regarding the safety of parenteral sedation in these populations.

Second, the monitoring used for research purposes (that is, expired carbon dioxide and electrocardiography) may exceed that usually found in dental practice settings for patients in whom conscious sedation is produced. Furthermore, at least one investigator trained in anesthesia was always present in addition to the oral surgeon, providing a level of professional vigilance not possible with an operator-anesthetist or a dental assistant working under the supervision of the clinician performing the procedure.

Third, the results of evaluations of prototypic drugs representative of the benzodiazepines, opioids and ultrashort-acting barbiturates may be extrapolated to the use of similar drugs from these classes, but are not relevant to the large number of unrelated drugs and diverse combinations of drugs in clinical use.[6] Additionally, each drug group consisted of about 200 patients, a sample size that is too small to estimate the incidence of morbidity for events that occur infrequently.

CONCLUSION

The long-term need for anesthesia and sedation in dentistry may diminish as the decreased incidence of dental caries and tooth loss lessens the occurrence of traumatic procedures during childhood and adolescence that contribute to dental phobia in adulthood. Nevertheless, fear of dentistry remains an important impediment to care for a large segment of the population,[28,29] and trained dentists will continue to be needed to provide safe and effective anesthesia and sedation for emotionally and physically challenged patients. ■

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